The present rejection is based on misinterpretations of Lizardi and of the claimed method. Lizardi does not disclose what is alleged in the Office Action and, as a result, the combination of Kingsmore et al. and Lizardi do not disclose or suggest what is presently claimed. This error renders the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of obviousness. In making a rejection under 35 U.S.C. § 103, the Patent Office is burdened with establishing that the cited art teaches or suggests each and every limitation of the claims. The present rejection does not meet this burden.

Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. Kingsmore et al. fails to disclose decoupling of the amplification target circle from the reporter binding primers. In fact, in the method of Kingsmore et al. the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

Lizardi discloses a method of amplifying or detecting nucleic acids by target-mediated ligation of linear open circle probes (to form circular amplification target molecules) followed by amplification of the amplification target circles by rolling circle amplification (see from column 2, line 53, to column 3, line 7). Lizardi was cited for its disclosure of removal of unligated (that is, linear, non-circular) open circle probes following target-mediated ligation of open circle

probes and before subsequent steps. For example, Lizardi discloses that unligated open circle probes can be digested with exonuclease to prevent them from interfering with rolling circle amplification (see, for example, column 24, lines 41-67). However, Lizardi fails to disclose or suggest decoupling of amplification target circles from reporter binding molecules. Thus, Lizardi fails to supplement the gap in the disclosure of Kingsmore et al.

Applicants claim a method of detecting analytes that involves, *inter alia*, association of reporter binding molecules (which each comprise a specific binding molecule and an amplification target circle) with analytes. The amplification target circles are replicated to produce tandem sequence DNA. Significantly, however, the amplification target circles are decoupled from the reporter binding molecules prior to replication.

Applicants submit that neither Kingsmore et al. nor Lizardi disclose any step of decoupling of an amplification target circle as required by the claims. The rejection admits that Kingsmore et al. fails to disclose decoupling of an amplification target circle as claimed. The passages of Lizardi cited in the rejection do not disclose decoupling of any amplification target circle from any reporter binding molecule. Rather, the cited passages disclose removal (not decoupling) of open circle probes (not amplification target circles) from a reaction mixture prior to subsequent steps.

A. Relevant to the passages of Lizardi cited in the rejection, Lizardi discloses a method that involves:

(a) mixing open circle probes with a target sample and incubating to promote hybridization between the open circle probes and the target sequences in the target sample,

(b) mixing ligase with the mixture and incubating to promote ligation of the open circle probes to form amplification target circles,

(c) mixing a rolling circle replication primer with the mixture and incubating to promote hybridization between the amplification target circles and the rolling circle replication primer, and

(d) mixing DNA polymerase with the mixture and incubating to promote replication of the amplification target circles, where replication of the amplification target circle results in the formation of tandem sequence DNA (see column 19, lines 41-65).

According to Lizardi, open circle probes are linear single-stranded DNA molecules having two target probe portions (one at each end) that are complementary to a target sequence such that, upon hybridization to the target sequence, the ends of the target probe portions (which are the ends of the open circle probe) are adjacent and can be ligated (see Figure 1, column 5, lines 22-25, column 6, lines 12-13 and 25-30). This ligation forms a circular open circle probe that Lizardi refers to as an amplification target circle (see column 9, lines 49-51).

Applicants note that in step (b) above the open circle probes, which are hybridized to target sequences, are ligated to form amplification target circles. The amplification target circles then serve as a template for replication to form tandem sequence DNA in steps (c) and (d). The passages of Lizardi cited in the rejection refer to removal of unligated open circle probes. That is, removal of those open circle probes that are not ligated in step (b) above. The removal passages in Lizardi are concerned with eliminating unligated open circle probes and retaining ligated open circle probes (see column 26, lines 32-35, column 24, lines 41-67, from column 34, line 57, to column 35, line 16). Unlike the ligated, circularized open circle probes, the unligated

open circle probes of Lizardi have free ends that are susceptible to exonuclease and are not topologically locked to the target sequence and so can be washed away (see from column 34, line 57, to column 35, line 16, column 33, lines 13-19). Significantly, the ligated open circle probes (which constitute amplification target circles) are not removed, eliminated or digested in Lizardi. They remain intact and associated with the target sequence to be replicated in situ (see Figure 4). Thus, the passages of Lizardi cited in the rejection do not involve any "decoupling" of amplification target circles and the removal of unligated open circle probes does not in any way suggest decoupling of amplification target circles as presently claimed. For at least these reasons, Kingsmore et al. and Lizardi fail to disclose or suggest the method of claims 1-136. Accordingly, Kingsmore et al. and Lizardi fail to make obvious the method of claims 1-136.

B. The claimed method requires replication of the amplification target circles after they are decoupled from the reporter binding molecules. As can be seen from the discussion above, and as is apparent from Lizardi, the unligated open circle probes that are eliminated in Lizardi are never replicated in the method of Lizardi and are removed specifically to prevent such unligated open circle probes from affecting replication of amplification target circles. Thus, the removed unligated open circle probes cannot constitute or suggest the claimed decoupling of amplification target circles because the allegedly "decoupled" component of Lizardi is never replicated and/or cannot be replicated in the method of Lizardi. For at least this additional reason, Kingsmore et al. and Lizardi fail to disclose or suggest the method of claims 1-136. Accordingly, Kingsmore et al. and Lizardi fail to make obvious the method of claims 1-136.

C. A rejection under 35 U.S.C. 103 cannot be sustained if the proposed modification would alter the fundamental principle of operation of the prior art to be modified. *In re Ratti*,

270 F.2d 810, 813, 123 USPQ 349(CCPA 1959). Modification of the method of Kingsmore et al. cited in the rejection as suggested in the rejection would change the principle of operation of the method and thus the present rejection cannot be sustained.

Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. In the method of Kingsmore et al. the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

In fact, if the amplification target circle was dissociated from the reporter binding primer prior to replication, the amplification target circle could not be replicated because such dissociation would separate the amplification target circle form the rolling circle replication primer (the primer is part of the reporter binding primer). Further, even if such a hypothetical dissociated amplification target circle was replicated using a different primer, this would defeat Kingsmore et al.'s purpose in having a rolling circle replication primer as part of a reporter binding primer. Kingsmore et al. states that:

> The method involves associating nucleic acid primer with the analyte and subsequently using the primer to mediate rolling circle replication of a circular DNA molecule. Amplification of the DNA circle is dependent on the presence of the primer. Thus, the disclosed method produces an amplified signal, via rolling circle amplification, from any analyte of interest. The amplification is isothermic

> and can result in the production of a large amount of nucleic acid from each primer. The amplified DNA remains associated with the analyte, via the primer, and so allows spatial detection of the analyte.

Column 4, lines 37-47 (emphasis added).

Dissociation of the amplification target circle would eliminate the intended connection between the analyte and the amplified DNA and thus eliminate the spatial detection of the analyte sought by Kingsmore et al. This alteration, required by the present rejection, would eliminate a major feature of the method of Kingsmore et al. Such a change in the principle of operation of the method of Kingsmore et al., which results from the modification proposed by the rejection, renders the rejection unsustainable. Accordingly, Kingsmore et al. and Lizardi fail to make obvious the method of claims 1-136.

Double Patenting Rejection

Claims 1, 12-113 and 118-136 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-72 of U.S. Patent No. 6,531,283 to Kingsmore et al. in view of U.S. Pat. No. 5,854,033 to Lizardi. Applicants respectfully traverse this rejection.

The present rejection is based on misinterpretations of Lizardi and of the claimed method. Lizardi does not disclose what is alleged in the Office Action and, as a result, the combination of Kingsmore et al. and Lizardi do not disclose or suggest what is presently claimed. This error renders the rejection legally flawed with the result that the Office Action fails to establish a prima facie case of obviousness-type double patenting. In making an obviousness-type double patenting rejection, the Patent Office is burdened with establishing that the cited patent teaches

or suggests each and every limitation of the claims. The present rejection does not meet this burden.

Claims 1-72 of U.S. Patent No. 6,531,283 (Kingsmore et al.) encompass methods of analyte detection that involve, *inter alia*, bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. None of the claims of Kingsmore et al. recite that the amplification target circle is decoupled from the reporter binding primers. In fact, the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

Lizardi discloses a method of amplifying or detecting nucleic acids by target-mediated ligation of linear open circle probes (to form circular amplification target molecules) followed by amplification of the amplification target circles by rolling circle amplification (see from column 2, line 53, to column 3, line 7). Lizardi was cited for its disclosure of removal of unligated (that is, linear, non-circular) open circle probes following target-mediated ligation of open circle probes and before subsequent steps. For example, Lizardi discloses that unligated open circle probes can be digested with exonuclease to prevent them from interfering with rolling circle amplification (see, for example, column 24, lines 41-67). However, Lizardi fails to disclose or

suggest decoupling of amplification target circles from reporter binding molecules. Thus, Lizardi fails to supplement the gap in the disclosure of Kingsmore et al.

Applicants claim a method of detecting analytes that involves, *inter alia*, association of reporter binding molecules (which each comprise a specific binding molecule and an amplification target circle) with analytes. The amplification target circles are replicated to produce tandem sequence DNA. Significantly, however, the amplification target circles are decoupled from the reporter binding molecules prior to replication.

Applicants submit that neither Kingsmore et al. nor Lizardi disclose any step of decoupling of an amplification target circle as required by the claims. The rejection admits that Kingsmore et al. fails to disclose decoupling of an amplification target circle as claimed. The passages of Lizardi cited in the rejection do not disclose decoupling of any amplification target circle from any reporter binding molecule. Rather, the cited passages disclose removal (not decoupling) of open circle probes (not amplification target circles) from a reaction mixture prior to subsequent steps.

A. Relevant to the passages of Lizardi cited in the rejection, Lizardi discloses a method that involves:

(a) mixing open circle probes with a target sample and incubating to promote hybridization between the open circle probes and the target sequences in the target sample,

(b) mixing ligase with the mixture and incubating to promote ligation of the open circle probes to form amplification target circles,

(c) mixing a rolling circle replication primer with the mixture and incubating to promote hybridization between the amplification target circles and the rolling circle replication primer, and

(d) mixing DNA polymerase with the mixture and incubating to promote replication of the amplification target circles, where replication of the amplification target circle results in the formation of tandem sequence DNA (see column 19, lines 41-65).

According to Lizardi, open circle probes are linear single-stranded DNA molecules having two target probe portions (one at each end) that are complementary to a target sequence such that, upon hybridization to the target sequence, the ends of the target probe portions (which are the ends of the open circle probe) are adjacent and can be ligated (see Figure 1, column 5, lines 22-25, column 6, lines 12-13 and 25-30). This ligation forms a circular open circle probe that Lizardi refers to as an amplification target circle (see column 9, lines 49-51).

Applicants note that in step (b) above the open circle probes, which are hybridized to target sequences, are ligated to form amplification target circles. The amplification target circles then serve as a template for replication to form tandem sequence DNA in steps (c) and (d). The passages of Lizardi cited in the rejection refer to removal of unligated open circle probes. That is, removal of those open circle probes that are not ligated in step (b) above. The removal passages in Lizardi are concerned with eliminating unligated open circle probes and retaining ligated open circle probes (see column 26, lines 32-35, column 24, lines 41-67, from column 34, line 57, to column 35, line 16). Unlike the ligated, circularized open circle probes, the unligated open circle probes of Lizardi have free ends that are susceptible to exonuclease and are not topologically locked to the target sequence and so can be washed away (see from column 34, line

57, to column 35, line 16, column 33, lines 13-19). Significantly, the ligated open circle probes (which constitute amplification target circles) are not removed, eliminated or digested in Lizardi. They remain intact and associated with the target sequence to be replicated in situ (see Figure 4). Thus, the passages of Lizardi cited in the rejection do not involve any "decoupling" of amplification target circles and the removal of unligated open circle probes does not in any way suggest decoupling of amplification target circles as presently claimed. For at least these reasons, Kingsmore et al. and Lizardi fail to disclose or suggest the method of claims 1, 12-113 and 118-136. Accordingly, Kingsmore et al. and Lizardi fail to make claims 1, 12-113 and 118-136 obvious variations pf claims 1-72 of Kingsmore et al.

B. The claimed method requires replication of the amplification target circles after they are decoupled from the reporter binding molecules. As can be seen from the discussion above, and as is apparent from Lizardi, the unligated open circle probes that are eliminated in Lizardi are never replicated in the method of Lizardi and are removed specifically to prevent such unligated open circle probes from affecting replication of amplification target circles. Thus, the removed unligated open circle probes cannot constitute or suggest the claimed decoupling of amplification target circles because the allegedly "decoupled" component of Lizardi is never replicated and/or cannot be replicated in the method of Lizardi. For at least this additional reason, Kingsmore et al. and Lizardi fail to disclose or suggest the method of claims 1, 12-113 and 118-136. Accordingly, Kingsmore et al. and Lizardi fail to make claims 1, 12-113 and 118-136 obvious variations pf claims 1-72 of Kingsmore et al.

C. A rejection under 35 U.S.C. 103 cannot be sustained if the proposed modification would alter the fundamental principle of operation of the prior art to be modified. *In re Ratti*,

270 F.2d 810, 813, 123 USPQ 349(CCPA 1959). Modification of the method of Kingsmore et al. cited in the rejection as suggested in the rejection would change the principle of operation of the method and thus the present rejection cannot be sustained.

Kingsmore et al. discloses a method for detecting analytes involving bringing analytes into contact with reporter binding primers, which are made up of a specific binding molecule and a rolling circle replication primer, such that the specific binding molecule binds to the analyte. An amplification target circle is brought into contact with the rolling circle replication primer (which is part of the reporter binding primer) and the amplification target circle is replicated via priming by the rolling circle replication primer, thus forming tandem sequence DNA. In the method of Kingsmore et al. the amplification target circle is associated with the reporter binding primer (via the rolling circle replication primer) prior to replication and remains associated with the reporter binding primer during replication.

In fact, if the amplification target circle was dissociated from the reporter binding primer prior to replication, the amplification target circle could not be replicated because such dissociation would separate the amplification target circle form the rolling circle replication primer (the primer is part of the reporter binding primer). Further, even if such a hypothetical dissociated amplification target circle was replicated using a different primer, this would defeat Kingsmore et al.'s purpose in having a rolling circle replication primer as part of a reporter binding primer. Kingsmore et al. states that:

> The method involves associating nucleic acid primer with the analyte and subsequently using the primer to mediate rolling circle replication of a circular DNA molecule. Amplification of the DNA circle is dependent on the presence of the primer. Thus, the disclosed method produces an amplified signal, via rolling circle amplification, from any analyte of interest. The amplification is isothermic

> and can result in the production of a large amount of nucleic acid from each primer. The amplified DNA remains associated with the analyte, via the primer, and so allows spatial detection of the analyte.

Column 4, lines 37-47 (emphasis added).

Dissociation of the amplification target circle would eliminate the intended connection between the analyte and the amplified DNA and thus eliminate the spatial detection of the analyte sought by Kingsmore et al. This alteration, required by the present rejection, would eliminate a major feature of the method of Kingsmore et al. Such a change in the principle of operation of the method of Kingsmore et al., which results from the modification proposed by the rejection, renders the rejection unsustainable. Accordingly, Kingsmore et al. and Lizardi fail to make claims 1, 12-113 and 118-136 obvious variations of claims 1-72 of Kingsmore et al.

For all of these reasons, the presently claimed decoupling of amplification target circles from reporter binding molecules is not an obvious variation of any step or operation in the claims of Kingsmore et al. For at least these reasons, present claims 1, 12-113 and 118-136 are not obvious variations of claims 1-72 of Kingsmore et al. Accordingly, the present rejection cannot be sustained.

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

It is believed that no fee is due with this submission. However, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

Robert A Hodges
Registration No. 41,074

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Robert A. Hodges — Date: 4/25/2005